

Amendments to the Specification:

Please replace the Examples Section beginning at page 52, line 16, with the following rewritten Examples Section:

EXAMPLES

Experiment 1.

The high-phosphatidylcholine lecithin Epikuron 200™ (from Lucas-Meyer), in the amount 0.351 grams, was combined with 0.371 gm of gentisic acid ethanolamine, 0.201 gm water, 0.156 gm glycerol, and 0.127 gm alpha-tocopherol, which upon mixing and equilibration formed a reversed cubic phase. This cubic phase was capable of solubilizing dantrolene sodium at body temperature. Thus, to 0.233 gm of this cubic phase was added 9 mg of dantrolene sodium, and after heating and then cooling to 37 C, the resulting cubic phase was clear, optically isotropic, and free of dantrolene crystals according to observation in the polarizing optical microscope and through crossed polarizing filters in a low-magnification (about 2x) optical setup.

Experiment 2.

The high-phosphatidylcholine lecithin Epikuron 200™, in the amount 0.351 grams, was combined with 0.314 gm of gentisic acid ethanolamine, 0.199 gm water, 0.146 gm glycerol, and 0.125 gm alpha-tocopherol, which upon mixing and equilibration formed a reversed cubic phase. This cubic phase was capable of solubilizing the trans-platinum antineoplastic compound trans-[Pt(II)Cl₂(NH₃)(thiazole)] at a level of about 2.4%. Thus, 0.028 gm of this platinum compound was added to the cubic phase, and upon equilibration substantially all of the platinum compound was dissolved in the cubic phase. This cubic phase has almost identical composition with that in Experiment 1, underscoring the versatility of this composition in solubilizing a range of difficult drugs. Furthermore, a small increase in the gentisic acid ethanolamine concentration yields a lamellar phase, which could be useful in forming liposomes capable of incorporating paclitaxel and other drugs.

Experiment 3.

This example exemplifies the usefulness of combining alpha-tocopherol with phospholipid, essential oil, and water (or water plus glycerol) mixtures. Approximately 0.17 gm of Epikuron 200, 0.7 gm essential oil of sweet basil, 0.25 gm of water, and 0.25 gm of glycerol were mixed and the mixture centrifuged. The resulting 3-phase system featured only a small middle, liquid crystalline phase, and was mostly excess oil and excess water/glycerol. Then, upon the addition of about 0.33 gm of alpha-tocopherol, the liquid crystalline phase took up much more material so that at equilibrium, it was approximately equal in volume to the excess aqueous and oil phases. This liquid crystalline phase was capable of solubilizing paclitaxel to a level of at least 5 mg/ml.

Experiment 4.

The high-phosphatidylcholine lecithin Epikuron 200™, in the amount 0.909 grams, was combined with 0.408 gm of essential oil of basil, 0.424 gm of essential oil of ginger, 0.586 gm water, to which was added 66 mg of the active Coenzyme Q10. Upon mixing and equilibrating the mixture formed a reversed cubic phase in which the Coenzyme Q10 was fully solubilized.

Experiment 5.

The high-phosphatidylcholine lecithin Epikuron 200™, in the amount 0.354 grams, was combined with 0.128 gm of linalool, 0.379 gm of gentisic acid ethanolamine, 0.090 gm of essential oil of vanilla, and 0.273 gm water. The resulting equilibrated mixture was a cubic phase. Linalool has recently undergone extensive toxicity investigation, and has been shown to be of extremely low toxicity, not only by oral but also by intramuscular and intraperitoneal routes. Since gentisic acid ethanolamine has been used for decades in injectable products at a level of 100 mg per injection, in particular in a parenteral nutrition product, this mixture is composed of extremely benign components for drug-delivery.

Experiment 6.

This example shows the effectiveness of the amino acid tryptophan in inducing reversed liquid crystalline phases in phosphatidylcholine systems. Epikuron 200, 0.549 grams, was

combined with 0.166 gm of glycerol and 0.318 gm of water, which forms a lamellar phase in excess water, but the addition of only 0.023 gm of L-tryptophan resulted in a reversed cubic phase. The active aliphatic acid can be solubilized to an appreciable extent in this cubic phase, for example.

Experiment 7.

An antibiotic of Antex Biologics referred to as LH Syn 01, which had been problematic to solubilize with traditional means. In the amount of 2.034 grams, was dissolved in 6.028 grams of essential oil of ginger, together with 6 mg of BHT and 5 mg of BHA as antioxidants. To 7.852 grams of this solution were added 8.746 grams of the high-phosphatidylcholine lecithin Epikuron 200™, and 4.687 grams of water. The mixture formed a reversed cubic phase on equilibration, with the LH syn 01 active fully solubilized.

Experiment 8:

~~In this experiment, essential oils of ginger and sweet basil were combined to solubilize the bioactive compound ubiquinone (a coenzyme Q10) in a phospholipid-rich reversed liquid crystal. Coenzyme Q10, in the amount of 66 mg, was solubilized in a mixture of 0.408 gm oil of basil and 0.424 gm oil of ginger. To this was added 0.909 gm of Epikuron 200 and 0.586 gm water. The Q10 was solubilized in the resulting reversed bicontinuous cubic phase liquid crystal.~~

Experiment 9 8.

In this example the antibacterial compound 8-hydroxyquinoline was solubilized in a cubic phase. An amount of 62 mg of 8-hydroxyquinoline was dissolved in 0.311 gm oil of peppermint, to which were added 0.392 gm of Epikuron 200, 0.160 gm of glycerol, and 0.221 gm of water. The quinoline compound was solubilized in the resulting reversed bicontinuous cubic phase.

It should also be mentioned that 8-hydroxyquinoline is approved by the FDA for use as an inactive excipient in injectable formulations. Thus, in a cubic phase such as this, the 8-HQ could play the role of co-solubilizer, which by introducing amino groups into the bilayer could have a substantial enhancing effect on the solubilization of a number of actives.

Experiment 10 9.

Epikuron 200, in the amount of 0.360 gm, 0.289 gm of ascorbyl palmitate, 0.141 gm of gentisic acid, 0.205 gm of aminocaproic acid, 0.106 gm of ethanolamine, and 0.461 gm water were combined and mixed thoroughly. The result was an opaque mix of undissolved crystals and one or more lipid-containing phases as determined by examination in a polarizing optical microscope that was equipped with phase contrast capabilities. An amount 0.517 gm of this mix was removed, and upon the addition of 0.109 gm of oil of ginger, all of the crystalline components dissolved and the result was a transparent reversed cubic liquid crystalline phase. Dantrolene sodium, in the amount of 3 mg, dissolved in this phase, which thus comprised a pharmaceutically-acceptable, lipid-based liquid crystalline solubilization matrix for this pharmaceutical compound.

Experiment 11 10.

The local anesthetic bupivacaine, in the free base form, and in the amount of 0.096 grams, was combined with 0.376 gm linalool, 0.375 gm Pluronic P103, and 0.354 gm water. This formed a reversed cubic phase that, upon uptake of a small amount of water, can coexist with excess water. Both linalool (a component of a number of essential oils) and Pluronic P103 are of extremely low toxicity, making this cubic phase an attractive candidate as a depot delivery system for the local anesthetic. Increasing the duration of action of bupivacaine could be an important boon in the treatment of wounds including surgical wounds. The high octanol-water partition coefficient of bupivacaine should cause the bupivacaine to release slowly into body fluids.

Experiment 12 11.

Gum benzoin (obtained from Penta Chemicals, the "Siam" variety the active (as a functional excipient) was solubilized at the level of 1.0% in a cubic phase consisting of ylangylang oil, Pluronic P103, and water. The cubic phase can furthermore be dispersed as microparticles, and coated with a variety of coatings as described in published PCT Patent Application PCT/US98/18639 which can be formulated in oral or parenteral drug formulations for increased drug absorption.